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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/080,713	COLMAN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/18/09 has been entered.

Applicants' Amendment and Response, filed 3/18/09. Claims 62, 87-90, 118-120, 131 and 133 are amended; claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed 3/18/09, has been considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 62-69, 71-86, 88-97 of copending Application No. 11/641,644. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to overlapping subject matter. The instant claims are directed to producing non-human transgenic mammals, by modifying the nuclear genome of a fibroblast or other somatic cell that has a sufficient lifespan to be useful in genetic modification, and utilizing the cell in methods of nuclear transfer. The '644 claims are drawn to methods of producing genetically modified ungulates by modifying the nuclear genome of a somatic cell with a normal karyotype at an endogenous locus, utilizing the somatic cell in nuclear transfer methods to produce a genetically modified ungulate. The instant claims recite utilizing fibroblasts as the nuclear donor, the '644 claims recite utilizing fibroblasts (claim 77, for example). Additionally, the instant claims are directed to any transgenic mammal, and further embodiments are directed to ungulates including sheep, pig, cattle, and goat (claim 63, for example). The instant claims and the '644 claims both claim inactivation of a gene (claim 66 in the instant application, claim 67 of the '644 Application). Additionally, both sets of claims recite modifying the nuclear genome of the donor cell to inactivate α-1,3 galactosyltransferase (claims 123-124 of the instant application; claims 68, 85, 97 of the '644 claims); And modifying an endogenous immunoglobulin gene (claim 125 of the instant application; claims 71, 86 of the '644 claims). Accordingly, the '644 claims are rendered obvious in view of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The amendment to the claims is found to introduce new matter into the as-filed disclosure. In particular, the claims have been amended to recite modifying the nuclear genome of a fibroblast-like cell that has a sufficient lifespan to be useful for genetic modification. However, the as-filed disclosure does not provide support for utilizing a fibroblast-like cell in the claimed methods. Additionally, dependent claims further limit the cell to an epithelial, fibroblast, endothelial or muscle cell (see claim 87, for example). There is no support in the as-filed disclosure that 1) these cells are considered "fibroblast-like" and that 2) that these fibroblast-like cells would be used as claimed in the instantly claimed methods.

To the extent that the claimed methods are not described in the instant disclosure, claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

Enablement

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

Methods for producing a non-human transgenic mammal, comprising:

(a) *in vitro* targeted modification of an endogenous gene in the nuclear genome of a fibroblast to produce a genetically modified fibroblast;

(b) transferring the genetically modified fibroblast, or the nucleus thereof, to an enucleated oocyte to produce a viable nuclear transfer unit;

(c) activating the viable nuclear transfer unit;

(d) culturing the viable nuclear transfer unit to produce an embryo;

(e) transferring the embryo to a final surrogate mother, which is a suitable host for the non-human mammal to be grown to term; and

(f) allowing embryo to develop to term, thereby producing a non-human transgenic mammal.

The specification does not reasonably provide enablement for the breadth of modifying the nuclear genome of any somatic cell, other than fibroblast.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the art recites using fibroblast or fibroblast-like cells, and therefore, amendment of the claims to a fibroblast or "fibroblast-like" cell overcomes the prior rejection of record. See p. 7 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. The specification provides no guidance for what a "fibroblast-like" cell encompasses, whether this cell would only require a fibroblast morphology, or would require any other features of a fibroblast. Given that the specification only discusses using fibroblasts, and the art only supports that only fibroblasts are enabled in methods of genetic targeting. Additionally, it is reiterated that although the art may discuss that cells are "fibroblast" or "fibroblast-like", there is no teaching in either the art, specification or evidence of record that provides specific

characterization of a "fibroblast-like" cell. That is, given that Applicants' provide no more guidance for characterizing their fibroblast cells than that of the art and Applicants have provided no more guidance than that which is found in the art with regard to the cells that have been used in Applicants' working examples. Additionally, it is noted that specific claims recite that the fibroblast or fibroblast-like cells are "epithelial, endothelial or muscle cells" (see claim 87). The specification does not provide enabling guidance for using any of these cell types, other than fibroblasts, in methods of specific gene targeting. The specification provides no guidance for how similar (or dissimilar) a cell must be in order to be considered *fibroblast-like* such that one of ordinary skill in the art would be able to identify this cell without undue experimentation. The Examiner has provided guidance for art-recognized qualities of fibroblasts (see p. 5 of the prior Office action, mailed 9/18/08). However, Applicants have not provided any guidance as to which qualities/characteristics of fibroblasts a cell must have, in order to be considered "fibroblast-like".

Finally, it is noted that the claims now recite utilizing a "fibroblast-like cell" that has sufficient lifespan to be useful for genetic modification. However, the specification does not provide any guidance to enable this amendment; particularly, the specification does not provide any guidance as to how to identify fibroblast-like cells that have a sufficient lifespan, and provided a specific definition for the phrase "sufficient lifespan". For example, does the cell need to divide sufficiently to provide a cell line, or does it need to be kept alive for a long time? Cells such as neurons do not divide, but certainly could have a long lifespan. The specification provides no guidance as to how to enable identification of a fibroblast-like cell that has a sufficient lifespan to be useful for genetic modification; therefore, this embodiment is not found to be enabled.

Accordingly, for the reasons cited above, it would have required undue experimentation for the skilled artisan to carry out the claimed methods, with a predictable degree of success, to implement the invention as claimed.

Claim Rejections - 35 USC § 112

The prior rejection of claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. The rejection to the claims is withdrawn in view of Applicants' amendment to the claim which now recites that the surrogate mother is a suitable host of the mammal to be grown to term.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "fibroblast-like" in claims 62, 90, 131 and 133 is a relative term which renders the claim indefinite. The term "fibroblast-like" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In particular, the metes and bounds of this term cannot be determined; the specification does not provide any specific definition for the phrase "fibroblast-like" such that one of skill in the art could recognize how similar or dissimilar a cell would be to a fibroblast in order to be considered "fibroblast-like".

Appropriate correction is required. Claims 63, 65, 66, 70-73, 75-79, 82, 87-89, 121-125 depend from claim 62. Claims 99, 100, 102-110, 113, 118-125 depend from claim 90.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 are rejected under 35 U.S.C. 102(b) as anticipated by Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS).

The Examiner has changed this rejection to a sole 102(b) rejection because Campbell provides each and every step required by the claims, and therefore, is an anticipatory reference. The Examiner responds to Applicants' arguments as they apply to the instant rejection, below.

Applicants' Arguments. Applicants argue that the claims are directed to the production of transgenic animals where the donor nuclear genome is modified at a

targeted site, and specifically that the nuclear genome is modified "at an endogenous locus by a genetic targeting event" and that this is the distinguishing feature of the invention. Applicants argue that Campbell do not teach anything of value, *i.e.*, anything more than the prior art, as it relates to the targeted genetic modification of donor nuclei. See p. 8, ¶1-2 of the Response.

Applicants argue that the art recognized that there were difficulties in targeting genetic events in somatic cells and thus these cells must be grown in culture for significant amounts of time to identify a targeted modification, and that thus, the art recognized that targeted genetic modification could not be used in animals produced through NT because the viability of the cells would be compromised by extended cultured. Applicants argue that this is supported throughout the specification and the art. Applicants argue that it was well known that the ability to target a gene, in contrast to randomly integrating it, was much lower then somatic cells than ES cells, and that primary cells have a lower frequency of homologous recombination than immortalized cells. In particular, the Surani Declaration recites various factors, including the process of genomic imprinting were considered major obstacles to the use of genetically targeted somatic cells before the present filing. Applicants cite Arbones, Finn, Thyagarajan, and Porter as support for their arguments.

Response to Arguments. These arguments have been fully considered, but are not persuasive.

1. Arbonnes. Arbonés shows that mouse myoblasts can be specifically targeted, and that the cells show the properties of normal cells, including morphology, ability to differentiate *in vitro*, stable diploid karyotype, inability to form colonies in soft agar, and lack of tumorigenicity in nude mice. See Abstract. There is nothing in Arbnonés that suggests that the somatic cells cannot be specifically targeted, given that they specifically teach specific targeting of mouse myoblasts.

2. Finn & Thyagarajan. Applicants argue that Finn & Thyagarajan shows that primary cells have a lower frequency of homologous recombination. It is noted that these pieces of art, although showing lower frequencies of homologous recombination, do not show that somatic cells cannot be targeted. In fact, these pieces of art show that somatic cells are capable of being targeted.

3. Porter. Applicants present Porter as support for their arguments that somatic cells cannot be specifically targeted. The Examiner notes that Porter, in no way, teaches against specific targeting in somatic cells. In fact, they state that although generation of cells homozygous for a targeted mutation requires two successive gene targeting experiments, "Despite these considerations, *several* somatic cell lines homozygous for targeted mutations have been generated, and experiments of this kind promise to be useful for the genetic analysis of many problems in cell biology." See p. 12229, 1st col., Gene Targeting in Somatic Cells, 1st ¶, last sentence, emphasis added. Applicants' cited passage discusses issues of gene targeting in somatic stem cells, and discuss the limited knowledge in targeting somatic stem cells, particularly in the context of autologous transplantation. Clearly, Porter show that somatic cell lines that are homozygous for targeted mutations have been made, and the passage cited by Applicants is directed specifically to targeting somatic stem cells (not the breadth of any somatic cell, as claimed by the instant invention) for autologous transplantation (not the production of non-human transgenic mammals, as instantly claimed).

4. The Surani Declaration has been considered. It is noted that this Declaration states that, "By 1999, the techniques of genetic targeting and cloning by nuclear transfer were both well known. Although genetic targeting was typically performed on embryonic stem cells or established cell lines, it had also been performed on somatic cells." See #5 of the Declaration. The Surani Declaration provides no more guidance than the instant specification, or Campbell, with regard to how to determine if a particular donor cell has been affected by the phenomenon

of genomic imprinting. The scope of the instant claims provide no method steps such that one of skill in the art would be able to discern between cells that could – or could not – be used as viable donors for nuclear transfer. Thus, this Declaration does not provide evidence to overcome the rejection of record, and nor is it within the scope of the claimed invention. It is noted that the fact that the art cited by Applicants provides guidance to show that somatic cells can be produced that have specific, targeted mutations provides sufficient guidance to the ordinary skilled artisan to make specific, targeted mutations in somatic cells, that could be used in methods of nuclear transfer.

As a whole, the art cited by Applicants provide sufficient guidance to show, with a reasonable expectation of success, that one of skill in the art could specifically target an endogenous locus using, for example, homologous recombination. Thus, it is maintained that the state of the art, in no way, teaches away from producing a somatic cell with a specific genetic targeting event.

Finally, it is noted that the art cited by Applicants is directed to the breadth of "somatic cells". There is nothing in the cited art of record that would teach away from or suggest that utilizing a fibroblast, or a “fibroblast-like” cell, as encompassed by the instant claims, in methods of specifically targeting an endogenous locus, such that it would not work. The art of record is far broader than the instant claim limitations, and therefore does not specifically address the instant claim limitations.

Accordingly, it is maintained that Campbell fulfills the limitations of the claims. There is nothing that distinguishes the claimed invention from that which is taught by Campbell. Particularly, Campbell teach that transgenic animals can be made, by using a cell such as a fibroblast. This is exactly what is claimed. Applicants have not distinguished their invention from that which is taught and suggested by Campbell. Although one of skill in the art would recognize the general problems of the art, with regard to gene targeting somatic cells, Campbell provides specific guidance as to the cell types to use, as well as the techniques to produce the

desired result. Campbell provides the requisite teachings to fulfill the claim limitations because they teach each method step required by the claims.

Applicants' Arguments. Applicants argue that the perceived difficulty in producing specifically targeted, genetically modified somatic cells is further highlighted by Suraokar and Bradley, which is a comment on the scientific publication that embodied the instant invention. In particular, Campbell revived hope that livestock could be genetically modified, however, until now, it had not been shown that it would be possible to specifically modify endogenous genes by cloning. Additionally, Applicants point to Piedrahita who shows that available techniques were "not likely" to lead to targeted genetic modifications in somatic cells that could be used for NT, and that "in the future" techniques may be found for producing such targeted animals. Until the date of the present invention, therefore, skilled artisans were still looking for proof that the present invention of gene targeting and nuclear transfer "would be possible". See p. 9 of the Response.

Applicants argue that, to be anticipating, a prior art reference must enable the claimed invention. If the disclosure is merely a starting point for experimentation and a substantial uncertainty remains as to the success, the reference is not anticipating. Applicants argue that Campbell does not provide any techniques to overcome the art-recognized difficulties in developing targeted transgenic animals via NT, and that their teaching is only the expression of a hoped for result, offering nothing further regarding techniques or inventive contributions that would have been considered clearly necessary by one of skill in the art to overcome the art recognized problems. Applicants argue that Campbell provides nothing more than a starting point for experimentation, and that given the art-recognized belief that somatic cells could not be useful in this process after targeting, substantial uncertainty remained that the process would be successful, therefore, apps argue that Campbell is not enabled for the process recited in teh claims. See pp. 9-10 of the Response.

Response To Arguments. These arguments have been fully considered, but are not persuasive. In particular, the art of record, and at the time of filing did not specifically teach that one could not target a somatic cell. Although the art of record shows that it could be done, but with lower frequencies than, for example, using immortalized cells or ES cells, there is no evidence that, using the techniques taught by Campbell, one could not arrive at the claimed invention.

Applicants argue that Campbell does not provide any techniques to overcome the art-recognized difficulties in gene targeting somatic cells, and provide art to support these arguments (see p. 14 of the Response), it is noted that the claims do not provide any steps that are distinguished from the teachings of Campbell. Therefore, the suggestion that Campbell is unpredictable, or non-enabling, suggests that Applicants' invention might similarly be unpredictable or non-enabling. The method steps, as instantly claimed, are not distinguished from the teachings of Campbell, and therefore, the prior rejection of record is maintained. If Applicant feels the art is not enabling, and the claims cannot be distinguished from the art, then Applicant's claims must also lack enablement. It is up to Applicant to amend the claims to be enabled and distinguish from the art. However, the effect is inherent in the art applied, as the case law states if an invention and the art have the same structure all properties of one will be found in the other. Applicant is encouraged to amend the claims to overcome the art. See also, MPEP ¶2121.01 which states in part that, "A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)." In the instant case, Campbell provides sufficient guidance to arrive at the claimed invention, because they teach utilizing the exact same cell type (fibroblast) as that which is instantly claimed, and teach the exact same method steps that are

instantly claimed to arrive at the claimed invention. The art at the time of the claimed invention showed that it would be possible to specifically target an endogenous locus of a somatic cell. Campbell teaches that somatic cells, such as fibroblasts, can be genetically modified at a specific locus, and can then be used a donor cell in NT methods in order to produce a non-human transgenic mammal. Therefore, it is maintained that Campbell's disclosure is enabling and anticipates the claimed invention.

Applicants' Arguments. Applicants' argue that Campbell fails as a reference under §103(a) for much the same reasons that it fails under §102, namely in that the reference provides no more than a hoped for result in a field in which the hoped for result was considered outside of the ability of the ordinarily skilled artisan. See p. 10 of the Response. Applicants argue that an "essential component" of the obviousness determination is the analysis of secondary indicia of non-obviousness, which include, among others, a long felt need and failure of others, skepticism of skilled persons prior to the invention, commercial success and copying of the invention. Applicants argue that it is evident from the cited art, including Campbell, the desirability of targeted genetically modified large animals, and that even after Campbell's filing, it took over four years to develop the presently claimed techniques to produce viable, genetically targeted animals using SCNT. Applicants argue that not only was there a long felt need for this invention, and extensive skepticism and failure in the art, but to Applicants' knowledge, all later authors publishing on genetically modified large animals have followed the techniques described in the present application.

Response to Arguments. Applicants' arguments have been fully considered, but are not persuasive. The Examiner has now maintained this rejection as a §102(b) rejection. Additionally, with regard to Applicants' arguments, it is noted that, MPEP §2141 states, in part that:

> ***The weight to be given any objective evidence is made on a case-by-case basis.*** The mere fact that an applicant has presented evidence

does not mean that the evidence is dispositive of the issue of obviousness.

Applicants' argue that they developed the presently claimed techniques over four years after Campbell's filing. It appears that the instant applicant has priority to 3/4/99, thus, only two years after Campbell's publication date. Additionally, it is unclear what "techniques" have been developed in the instant application that distinguishes Applicants' invention from that which is taught in Campbell. The claims provide no indication of any technique that differentiates the instant invention from that taught by Campbell. That is, because Campbell teaches each component of the claimed method, they anticipate the claimed invention. The instant invention requires no more than what is taught in Campbell. Clearly, if Applicants' invention addresses a long felt need, it would need to overcome an art-recognized problem. Applicants' argue that the art-recognized problem is that somatic cells could not be specifically targeted. However, the art clearly teaches that it is possible to produce somatic cells with specific gene targeting. Additionally, assuming that this is an art-recognized problem, Applicants have not provided any evidence as to how this art-recognized problem was overcome, because the art of Campbell and the claimed method are not distinguished, each from the other.

Accordingly, this rejection is maintained.

Claims 62, 63, 65, 66, 75, 82, 87-90, 99, 100, 106, 113, 118-122, 131 and 133 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 6,147,276 (Issued November 14, 2006, filed February 19, 1997).

Regarding claims 62, 90, 131 and 133, the '276 patent teaches methods of nuclear transfer to produce transgenic mammals (Abstract). The '276 patent teaches that donor cells can be fibroblasts (col. 4, lines 10-11). The '276 patent teaches producing cloned animals by transferring the donor cell nucleus into an

enucleated metaphase II oocyte (col. 5, lines 58+), the activation of the resultant NT unit (col. 6, lines 63+) and developing a cloned animal from the embryo (col. 7, lines 35-44). The '276 patent teaches that transgenic animals can be produced by the claimed methods (col. 3, lines 16-20).

Regarding claim 63, the '276 patent teaches producing sheep, goat, camels, pigs (col. 3, lines 6-9).

Regarding claims 65, 66, 99, 100, the '276 patent teaches that endogenous genes can be deleted, duplicated, activated or modified (col. 3, lines 43-54 and col. 10, lines 43-49).

Regarding claims 75, 76, 106 the '276 patent teaches that transgenesis may be employed with selectable markers (col. 10, lines 47-49).

Regarding claims 82, 113, the '276 patent teaches that the genetic modification can be produced by lipofection (col. 4, lines 63-64).

Regarding claims 87, 118, the '276 patent teaches utilizing fibroblasts as donor cells (col. 4, lines 10-11).

Regarding claims 88, 89, 119, 120, the '276 document teaches inducing quiescence and arrest the cells in G0 phase of the cell cycle by serum starvation (col. 9, lines 39-41; col. 10, lines 17-18).

Regarding claims 121, 122, the '276 document teaches transfection by electroporation (col. 3, lines 60-64).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 62, 63, 65, 66, 75-79, 82, 87-90, 99, 100, 106-110, 113, 118, 119, 120-124, 131 and 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of d'Apice *et al.* (**U.S. Pat. No.** 5,849,991 published December 15, 1998).

Response to Arguments. Applicants have provided the same arguments with regard to Campbell, which have been addressed above. Applicants argue that d'Apice discuss providing homozygous mice that lack a particular gene, alpha 1-3, galactosyltransferase, using ES cells. Applicants argue that the instant invention is directed to producing cloned animals with a targeted genetic modification, which differs dramatically from the type of random integration that can produce a transgenic animal without selection. See p. 11-12 of the Response. Applicants argue that d'Apice provide discussions focused upon ES cell technology and do not discuss the problem in the art with regard to targeted genetic modification of somatic cells for nuclear transfer, and that because ES cells were not available, there is no teaching in d'Apice to overcome the hurdles in the art associated with the use of targeted, genetically modified somatic cells as nuclear donors. Applicants

argue that d'Apice does nothing to address the serious art-recognized problems associated with targeted genetic modification in combination with SCNT that are not addressed in Campble, and that d'Apice relies upon ES cell technology, which to this day has not been enabled due to lack of large animal ES cells, therefore the skilled artisan reading Campbell alone, or in combination with d'Apice would not believe that a viable animal with a targeted genetic event could be produced using the techniques recited in the amended claims. See pages 12-13 of the Response.

Response to Arguments. The Examiner notes that the claims recite modifying an endogenous locus by a genetic targeting event. The broadest interpretation of this claim encompasses either random or non-random integration events. The term "targeting" does not mean that a locus is specifically targeted, for example, by method of homologous recombination. The claims read on any genetic modification, by any method of genetic targeting. The claims do not recite utilizing homologous recombination to produce the targeting event. The claims do not distinguish a specific, genetic modification at a specific endogenous locus, versus a random integration into an endogenous locus. Furthermore, the Examiner notes that d'Apice is not relied upon with regard to producing animals by NT. Campbell provides the required teachings for producing transgenic mammals via NT, and d'Apice discusses producing mammals, including but not only, mice, lacking alpha 1-3 galactosyltransferase (col. 4, lines 54-60). Additionally, it is noted that the claims are not limited to "large animals" but are directed to any non-human transgenic mammal. Therefore, the combination of the references sufficiently motivate the skilled artisan to arrive at the claimed invention, given Campbell's teachings for increasing efficiency of producing transgenic animals, and further, given d'Apice's teachings for the need in the art to produce animals whose organs can then be used for xenotransplantation, wherein the knockout of the alpha 1-3 galactosyltransferase gene reduces or eliminates the hyperacute rejection response.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 70, 73, 75-77, 82, 87-90, 99, 100, 102, 105-108, 113, 118-122, 125, 131, 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Kucherlapati *et al.* (**WO 94/02602**, published February 3, 1994).

Response to Arguments. Applicants have provided the same arguments with regard to Campbell and d'Apice, which have been addressed above. These arguments are not persuasive. Campbell is used to provide guidance to producing cloned, transgenic animals. The Examiner notes that the claims are not solely limited to large animals. Therefore, the combination of references sufficient motivate the skilled artisan to arrive at the claimed invention. Accordingly, given the combined teachings of Campbell and Kuncherlapati, it would have been obvious for one of ordinary skill in the art to use the technology of Campbell, and inactivate an endogenous Ig gene in a somatic cell, with a reasonable expectation of success. Although Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, Campbell provides the teachings and suggestion to use a somatic cell, and then use the modified somatic cell in methods of NT to produce transgenic animals. One of ordinary skill in the art would have been sufficiently motivated to knockout an endogenous Ig gene, as supported by Kuncherlapati, who teach that it is an art-recognized goal to produce xenogeneic specific binding proteins, such as human monoclonal antibodies (p. 2, lines 23-32) by production of transgenic animals. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by Kuncherlapati, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize

utilizing various marker genes in order to select for clones when performing transfection experiments.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 70, 72, 75, 76, 82, 87-90, 99, 100, 102, 104, 106, 113, 118-122, 131 and 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of US Pat. No. 6,013,857 (Filed June 5, 1995, Issued January 11, 2000).

Response to Arguments. Applicants argue that Bedalov discuses the COL1A1 promoter fused to a reporter gene in a variety of mesenchymal cell types, and that this reference does not provide any guidance with regard to issues of targeted gene modification and so would not alter the lack of expectation of success in the claimed techniques based on Campbell. The Examiner has responded to Campbell above.

Accordingly, it would have been obvious for one of ordinary skill in the art, to modify the methods, as taught by Campbell, to place a transgene of interest adjacent to an endogenous promoter, such as a milk promoter, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification, in view of the '857 patent which teaches that these methods would be used in order to produce recombinant polypeptides of interest from transgenic bovine species and isolate the recombinant polypeptide from milk (Abstract).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 70, 71, 75, 76, 82, 87-90, 99, 100, 102, 103, 106, 113, 118, 119, 120-122, 131 and 133 stand rejected under 35 U.S.C. 103(a) as being

unpatentable over Campbell in view of Bedalov (**Journal of Biol. Chem.**, 269(7): 4903-4909, 1994) when taken with Rossert (**The J. of Cell Biol.** 129(5): 1421-1432, 1995).

Applicants provide the same arguments regarding Campbell and Bedalov. The Examiner has addressed these arguments above.

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome wherein the promoter is a collagen gene promoter. However, prior to the time of the claimed invention, Bedalov discuss a transgene containing the COL1A1 promoter fused to a reporter gene and discuss its expression in a variety of mesenchymal cell types, including fibroblasts, osteoblasts and odontoblasts (see p. 4903, 1st col., 1st ¶). Bedalov teaches that transgenic mice which have ~3.5 kb of COL1A1 upstream promoter have strong expression of the reporter gene in high collagen producing tissues, such as tendon, bone and skin (p. 4903, col. 2, first full ¶). Bedalov teach that the COL1A1 construct, including the COL1A1 promoter confers tissue-specific expression in transgenic animals, with no aberrant expression (see pp. 4908-4909, bridging sentence). Bedalov suggest that making transgenic animals with genome-integrated transgenes would allow for further analysis of endogenous gene expression and would provide a model that is more biologically representative for the interaction of trans-acting factors with the sequences in the promoter (p. 4909, 1st full ¶, last sentence).

Accordingly, it would have been obvious for one of ordinary skill in the art, to utilize the teachings to make a transgenic, gene targeted animal, by nuclear transfer, as taught by Campbell, and specifically target a transgene under the expression of a collagen promoter, such as that taught by Bedalov, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Bedalov's teachings, which show an art-recognized need to further analyze the expression of the COL1A1

promoter in transgenic animals, and additionally, in view of Rossert, who teach that the precise sequences responsible for the lineage-specific expression of the collagen promoter have not been defined (p. 1421, col. 2, last bridging ¶). Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632